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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,363	08/21/2003	Xian-Ming Zeng	NHC19586-USA	8633

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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 03/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/646,363	ZENG, XIAN-MING	
	Examiner	Art Unit	
	James H. Alstrum-Acevedo	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-15 are pending. Acknowledgement is made of receipt of Applicant's election of Group I (claims 1-10) with traverse in the response submitted on February 6, 2006.

Election/Restrictions

The restriction requirement is hereby withdrawn, in view of the Examiner's observation that the search of the elected group was coextensive with the search of the non-elected groups.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in the United Kingdom on August 21, 2002. It is noted, however, that applicant has not filed a certified copy of the 0219511.3 application as required by 35 U.S.C. 119(b).

Specification

The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

The disclosure is objected to because of the following informalities: a space should be inserted between the words "uniformity" and "is" on line 2 of [0018].

Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trofast (U.S. Patent No. 6,030,604).

The teachings of Trofast do not anticipate the cited claims of the instant invention, because these teachings do not expressly recite the same order of mixing of ingredients.

Trofast teaches **dry powder composition** comprising **one or more** potent **pharmaceutically active substances** and **a carrier substance**, all of which are in finely divided form, useful in the treatment of respiratory disorders (abstract).

Trofast teaches that the active substance for use in his invention is preferably a glucocorticosteroid, including **budesonide** (col. 1, lines 38-39, 45, and 49). The carrier substance is preferably a mono-, di-, or polysaccharide, including **lactose** (a disaccharide), wherein lactose is preferred (col. 1, lines 64-66 and col. 2, lines 1-2). **The combination of budesonide and formoterol fumarate dihydrate** is particularly preferred (col. 2, lines 11-13). The **molar ratio of formoterol to budesonide in the formulation is preferably from 1:2,500 to 12:1** (col. 2, lines 16-18).

Trofast teaches a method of preparing the formulations of his invention comprising the steps of (a) **micronizing one or more potent pharmaceutically active substances and the carrier substance**; (b) optionally conditioning the product; and (c) spheronizing until the desired bulk density is obtained (col. 2, lines 50-58). The process of micronizing would obviously result in the mixing of the combined components. In Example 6, formoterol fumarate dihydrate is mixed with lactose monohydrate in a tumbling mixture, micronized, and the resulting product treated. The formoterol/lactose mixture is subsequently combined with micronized budesonide, mixed, remicronized, and agglomerated.

Trofast teaches that the formulations of his invention may be **administered using any known dry powder inhaler, including a multi-dose inhaler** (e.g. TURBOHALER®) (col. 3, lines 20-24).

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention that practice of Trofast teachings could yield the compositions of the instant application. Although Trofast does not expressly teach the step of adding a second portion of a first medicament, it would have been apparent to a skilled artisan that one could add additional

active agent as needed. Furthermore, it is noted that the step of mixing components in a method of making a pharmaceutical dry powder is conventionally practiced in the art. It is obvious that the order of mixing ingredients in a composition and the relative amount of ingredients in a composition are clearly result specific parameters. The amount of a specific ingredient in a composition and the order of steps in a process are clearly result effective parameters that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed and the optimal order of combining said ingredients to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts and the order of mixing ingredients would have been obvious at the time of applicant's invention. It would have been apparent to a skilled artisan that the composition taught by Trofast is comprised of inhalable particles, because Trofast teaches that his formulations may be administered using a multi-dose dry powder inhaler.

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sarlikiotis et al. (U.S. Patent No. 6,284,287).

The teachings of Sarlikiotis do not anticipate the cited claims of the instant invention, because these teachings do not expressly recite the same order of mixing of ingredients.

Sarlikiotis teaches a **pharmaceutical formulation for administration by inhalation**, a **micronized active compound or micronized active compound mixture** with a mean particle

size of 0.1 microns to 10 microns applied to a **pharmaceutically acceptable excipient** having a mean particle size of 200 microns to 1000 microns without the use of binders (abstract).

Sarlikiotis teaches that it has surprisingly been found that by **suitable mixing of the active compound or of the active compound mixture with a pharmaceutically utilizable excipient** which has a mean particle size of 200 microns to 1000 microns, the active compound particles having a particle size of 0.01 microns to 10 microns adhere to the excipient particles and thereby almost round **excipient particles coated with active compound result** (col. 2, lines 56-64).

Sarlikiotis teaches that his formulation may contain various active compounds including **anti-inflammatory substances** (e.g. **budesonide** and fluticasone) and **bronchodilators** (e.g. **formoterol**). The active compounds can be employed as free bases or acids or as **pharmaceutically tolerable salts**, including **fumarate salts**. Esters may also be employed (col. 3, lines 24-28, 38-39, 42-44, 55-65). The formulation may also consist of **a mixture of several finely ground active compounds** (col. 3, lines 66-67 and col. 3, line 1). The excipient employed in Sarlikiotis' formulations has a mean particle size of 200 microns to 1,000 microns and may be a disaccharide (e.g. **lactose**) (col. 4, lines 5-6 and 12-13). The ratio of active to excipient depends on the materials used. Exemplary formulations may include **10 to 80% active by weight to 20-90% excipient by weight** (col. 4, lines 18-25).

Sarlikiotis teaches that his invented formulations are prepared by mixing the constituents in a suitable mixer **until the excipient crystals are coated with the fine active compound or**

active compound mixture (col. 4, lines 32-33 and 38-40). Example 4 teaches the preparation of a composition comprising budesonide (30 g) and lactose (270 g).

It would have been apparent to a person of ordinary skill in the art at the time of the instant invention that the teachings of Sarlikiotis are obvious over the cited claims of the instant application, because Sarlikiotis teaches pharmaceutical compositions wherein an excipient (e.g. lactose) is coated by active agent or a mixture of active agents. Sarlikiotis recites that both budesonide and formoterol (e.g. as the fumarate salt) are suitable active agents, which may be present in the compositions of his invention. Furthermore, Sarlikiotis teaches that the compositions are made by mixing the excipient with the active agents, in such a manner to result in the coating of excipient particles with active agent.

Although Sarlikiotis does not expressly teach the step of adding a second portion of a first medicament, it would have been apparent to a skilled artisan that one could add additional active agent as needed. Furthermore, it is noted that the step of mixing components in a method of making a pharmaceutical dry powder is conventionally practiced in the art. It is obvious that the order of mixing ingredients in a composition and the relative amount of ingredients in a composition are clearly result specific parameters. The amount of a specific ingredient in a composition and the order of steps in a process are clearly result effective parameters that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed and the optimal order of combining said ingredients to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed

parameters, the optimization of ingredient amounts and the order of mixing ingredients would have been obvious at the time of applicant's invention.

Claims 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over of Sarlikiotis et al. (U.S. Patent No. 6,284,287) in view Clarke et al. (US 2002/0103260).

The teachings of Sarlikiotis have been set forth above.

Sarlikiotis lacks the teaching of a composition comprising formoterol fumarate dihydrate, a MDPI containing the compositions of the instant invention, and a method of administration comprising inhaling a pharmaceutical composition from a MDPI.

Clarke teaches a pharmaceutical composition comprising (A) **formoterol or a pharmaceutically acceptable salt thereof or a solvate of formoterol or said salt** and (B) fluticasone propionate, suitable for use in the treatment of inflammatory or obstructive airways diseases (abstract).

Clarke teaches the formoterol, particularly its **fumarate salt**, is a bronchodilator used in the treatment of inflammatory or obstructive airways diseases [0002].

Clarke teaches that it a significant unexpected therapeutic benefit synergistic therapeutic **benefit in the treatment of inflammatory or obstructive airways diseases** has surprisingly been found by using a composition containing formoterol, or a salt or solvate thereof, and fluticasone propionate [0003].

Clarke teaches that his invention provides a pharmaceutical composition comprising (A) formoterol or a pharmaceutically acceptable salt thereof or a solvate of formoterol or said salt and (B) fluticasone propionate [0004]. Preferably, component (A) is **formoterol fumarate dihydrate** [0010]. Administration of Clarke's invented formulation is preferably by **inhalation** [0011]. In one embodiment of Clarke's invention, the composition is in the form of **an inhalable dry powder** optionally together with a pharmaceutically acceptable carrier, including lactose. The dry powder may be contained in a reservoir of a **multi-dose dry powder inhalation device** (i.e. in a MDPI) [0012]. The carrier, if present, generally has a maximum size of 300 microns [0013]. The **weight ratio of formoterol or salt or solvate thereof to fluticasone propionate may be from 3:1 to 1:3,000** [0016]. A large number of exemplary compositions comprising lactose, formoterol fumarate dihydrate, and fluticasone propionate are provided in Examples 2-92. As evidenced by the cited examples taught by Clarke the ratio of bronchodilator to lactose carrier and steroid (i.e. fluticasone propionate) to lactose are always different, and the steroid is always present in a greater amount than the bronchodilator.

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Sarlikiotis and Clarke, because both inventors teach compositions intended for the treatment of respiratory disorders comprising a bronchodilator and an anti-inflammatory steroid. Although, Clarke teaches fluticasone propionate as the anti-inflammatory steroid it would have been apparent to a skilled artisan that one could substitute fluticasone for budesonide, because both compounds are anti-inflammatory corticosteroids used in inhalable formulations (Sarlikiotis). A person of ordinary skill in the art at the time of the instant invention would have had a reasonable expectation of success upon combination of the

prior art references, because both inventors teach similar compositions comprising an anti-inflammatory steroid, bronchodilator, and lactose carrier per the teaching set forth above. It would also have been apparent to a skilled artisan that one could administer via inhalation a composition comprising lactose, budesonide, and formoterol fumarate dihydrate from a MDPI, because Clarke teaches that compositions may be contained within a MDPI, an inhalation device, and Sarlikiotis teaches particulate formulations for administration by inhalation, as evidenced by the title of the Sarlikiotis reference.

Although Sarlikiotis does not expressly teach the step of adding a second portion of a first medicament, it would have been apparent to a skilled artisan that one could add additional active agent as needed. Furthermore, it is noted that the step of mixing components in a method of making a pharmaceutical dry powder is conventionally practiced in the art. It is obvious that the order of mixing ingredients in a composition and the relative amount of ingredients in a composition are clearly result specific parameters. The amount of a specific ingredient in a composition and the order of steps in a process are clearly result effective parameters that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed and the optimal order of combining said ingredients to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts and the order of mixing ingredients would have been obvious at the time of applicant's invention.

Other Matter

The Examiner noted that the indefinite article "an" was used improperly with the word "first." The indefinite article "an" is properly used when it precedes a word beginning with a vowel. Words beginning with a consonant should be preceded by the indefinite article, "a." The Examiner respectfully suggests changing "an" in claim 1, line 3 to "a." It was noted that the word "claim" was capitalized in claims 2-10 and 12-15. The Examiner respectfully suggests replacing the capitalized "Claim" as stated in claims 2-10 and 12-15 with "claim."

Conclusion

The specification is objected. All claims are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James H. Alstrum-Acevedo, Ph.D.
Examiner

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER